

|   |                        |                         |
|---|------------------------|-------------------------|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br>( Not for submission under 37 CFR 1.99) | Application Number     | 10616659                |
|   | Filing Date            | 2003-07-09              |
|   | First Named Inventor   | MARANAS, COSTAS D.      |
|   | <b>Art Unit</b>        | 1631                    |
|   | Examiner Name          | SKOWRONEK, KARLHEINZ R. |
|   | Attorney Docket Number | P06367US03 (1 OF 2)     |

| U.S.PATENTS       |         |               |                        |            |   |  |
|-------------------|---------|---------------|------------------------|------------|---|--|
| Examiner Initial* | Cite No | Patent Number | Kind Code <sup>1</sup> | Issue Date | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear |
| /KRS/             | 1       | 4520103       |                        | 1985-05-28 | Ensley, Jr., B.                                 |  |
| /KRS/             | 2       | 6117108       |                        | 2000-09-12 | Woehr et al.                                    |  |

If you wish to add additional U.S. Patent citation information please click the Add button.

| U.S.PATENT APPLICATION PUBLICATIONS |         |                    |                        |                  |   |  |
|-------------------------------------|---------|--------------------|------------------------|------------------|---|--|
| Examiner Initial*                   | Cite No | Publication Number | Kind Code <sup>1</sup> | Publication Date | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear |
|                                     | 1       |                    |                        |                  |   |  |

If you wish to add additional U.S. Published Application citation information please click the Add button.

| FOREIGN PATENT DOCUMENTS |         |                                      |                             |                        |                  |   |  |                          |
|--------------------------|---------|--------------------------------------|-----------------------------|------------------------|------------------|---|--|--------------------------|
| Examiner Initial*        | Cite No | Foreign Document Number <sup>3</sup> | Country Code <sup>2</sup> j | Kind Code <sup>4</sup> | Publication Date | Name of Patentee or Applicant of cited Document | Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear | T <sup>5</sup>           |
| /KRS/                    | 1       | JP 2000-268018                       | JP                          |                        | 1999-03-16       | Nippon Telegr & Teleph Corp                     |  | <input type="checkbox"/> |
| /KRS/                    | 2       | WO 98/18814                          | WO                          |                        | 1998-05-07       | Cumulative Inquiry                              |  | <input type="checkbox"/> |

|   |                      |                     |                         |  |
|---|----------------------|---------------------|-------------------------|--|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br>( Not for submission under 37 CFR 1.99) | Application Number   |                     | 10616659                |  |
|   | Filing Date          |                     | 2003-07-09              |  |
|   | First Named Inventor |                     | MARANAS, COSTAS D.      |  |
|   | Art Unit             |                     | 1631                    |  |
|   | Examiner Name        |                     | SKOWRONEK, KARLHEINZ R. |  |
| Attorney Docket Number  |                      | P06367US03 (1 OF 2) |                         |  |

|       |   |              |    |  |            |                                    |  |                          |
|-------|---|--------------|----|--|------------|------------------------------------|--|--------------------------|
| /KRS/ | 3 | WO 00/18906  | WO |  | 2000-04-06 | Maxygen                            |  | <input type="checkbox"/> |
| /KRS/ | 4 | WO 00/42559  | WO |  | 2000-07-20 | Maxygen                            |  | <input type="checkbox"/> |
| /KRS/ | 5 | WO 01/90346  | WO |  | 2001-11-29 | California Institute of Technology |  | <input type="checkbox"/> |
| /KRS/ | 6 | WO 04/018621 | WO |  | 2004-04-03 | Penn State Research Foundation     |  | <input type="checkbox"/> |

If you wish to add additional Foreign Patent Document citation information please click the Add button

#### NON-PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T <sup>5</sup>           |
|--------------------|---------|---|--------------------------|
| /KRS/              | 1       | Arigoni, et al., "A genome-based approach for the identification of essential bacterial genes," Nat. Biotechnol. 16 (9):851-856 (1998).   | <input type="checkbox"/> |
| /KRS/              | 2       | Aristidou et al., "Modification of central metabolic pathway in Escherichia coli to reduce acetate accumulation by heterologous expression of the Bacillus subtilis acetolactate synthase gene," Biotechnol. Bioeng. 44:944-951 (1994).                         | <input type="checkbox"/> |
| /KRS/              | 3       | Arita, "Metabolic construction using shortest paths," Sim. Pract. Theory, 8(1-2):109-125 (2000).  | <input type="checkbox"/> |
| /KRS/              | 4       | Arita, "The metabolic world of Escherichia coli is not small," Proc. Natl. Acad. Sci. USA 101(6):1543-1547 (2004).  | <input type="checkbox"/> |
| /KRS/              | 5       | Bailey et al., "Combining evidence using p-values: application to sequence homology searches," Bioinformatics 14 (1):48-54 (1998)   | <input type="checkbox"/> |

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**  
( Not for submission under 37 CFR 1.99)

|                        |                         |
|------------------------|-------------------------|
| Application Number     | 10616659                |
| Filing Date            | 2003-07-09              |
| First Named Inventor   | MARANAS, COSTAS D.      |
| Art Unit               | 1631                    |
| Examiner Name          | SKOWRONEK, KARLHEINZ R. |
| Attorney Docket Number | P06367US03 (1 OF 2)     |

|       |    |  |                          |
|-------|----|--|--------------------------|
| *     | 6  | Bhaskar, et al., "Applications of Multiobjective Optimization in Chemical Engineering," Rev. Chem. Eng. 16(1):1-54 (2000).   | <input type="checkbox"/> |
| /KRS/ | 7  | Blattner, et al., "The complete genome sequence of Escherichia coli K-12," Science 277(5331):1453-74 (1997).   | <input type="checkbox"/> |
| /KRS/ | 8  | Bogarad et al., "A hierarchical approach to protein molecular evolution," Proc. Natl. Acad. Sci. USA 96(6):2591-2595 (1999).   | <input type="checkbox"/> |
| /KRS/ | 9  | Bond et al., "Electricity production by Geobacter sulfurreducens attached to electrodes," Appl. Environ. Microbiol. 69 (3):1548-1555 (2003).   | <input type="checkbox"/> |
| *     | 10 | Burgard et al., "Optimization-based framework for inferring and testing hypothesized metabolic objective functions," Biotechnol. Bioeng. 82(6):670-677 (2003).   | <input type="checkbox"/> |
| /KRS/ | 11 | Burgard et al., "Optknock: a bilevel programming framework for identifying gene knockout strategies for microbial strain optimization," Biotechnol. Bioeng. 84(6):647-657 (2003).                      | <input type="checkbox"/> |
| /KRS/ | 12 | Castellanos et al., "A modular minimal cell model: purine and pyrimidine transport and metabolism," Proc. Natl. Acad. Sci. USA 101(17):6681-6686 (2004).   | <input type="checkbox"/> |
| /KRS/ | 13 | Causey et al., "Engineering Escherichia coli for efficient conversion of glucose to pyruvate," Proc. Natl. Acad. Sci. USA 101(8):2235-2240 (2004).   | <input type="checkbox"/> |
| /KRS/ | 14 | Chen et al., "Computer Program for Calculating the Melting Temperature of Degenerate Oligonucleotides Used in PCR or Hybridization," BioTechniques, 22:1158-1160 (1997).                               | <input type="checkbox"/> |
| /KRS/ | 15 | CHISTOSERDOVA et al., "Multiple formate dehydrogenase enzymes in the facultative methylotroph Methylobacterium extorquens AM1 are dispensable for growth on methanol," J. Bacteriol. 186:22-28 (2004). | <input type="checkbox"/> |
| /KRS/ | 16 | Cho et al., "Ethical considerations in synthesizing a minimal genome," Science 286:2087-2090 (1999).   | <input type="checkbox"/> |

|   |                        |                         |                     |
|---|------------------------|-------------------------|---------------------|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br>( Not for submission under 37 CFR 1.99) | Application Number     |                         | 10616659            |
|   | Filing Date            |                         | 2003-07-09          |
|   | First Named Inventor   | MARANAS, COSTAS D.      |                     |
|   | Art Unit               |                         | 1631                |
|   | Examiner Name          | SKOWRONEK, KARLHEINZ R. |                     |
|   | Attorney Docket Number |                         | P06367US03 (1 OF 2) |

|       |    |  |                          |
|-------|----|--|--------------------------|
| /KRS/ | 17 | Covert et al., "Metabolic modeling of microbial strains in silico," Trends Biochem. Sci. 26:179-186 (2001).  | <input type="checkbox"/> |
| /KRS/ | 18 | Das et al., International Journal of Hydrogen Energy, 26:13-28 (2001).   | <input type="checkbox"/> |
| /KRS/ | 19 | David et al., "Reconstruction of the central carbon metabolism of Aspergillus niger," Eur J. Biochem. 270 (21):4243-4253 (2003).                           | <input type="checkbox"/> |
| /KRS/ | 20 | Delgado et al., "Identifying Rate-Controlling Enzymes in Metabolic Pathways without Kinetic Parameters," Biotechnol. Prog. 7:15-20 (1991).                 | <input type="checkbox"/> |
| /KRS/ | 21 | Demain, "Stunning achievements of industrial microbiology," ASM News 65:311-316 (1999).  | <input type="checkbox"/> |
| /KRS/ | 22 | Edwards et al., "How will bioinformatics influence metabolic engineering?," Biotechnol. Bioeng. 58(2-3):162-169 (1998).                                    | <input type="checkbox"/> |
| /KRS/ | 23 | EDWARDS et al., "Metabolic flux balance analysis and the in silico analysis of Escherichia coli K-12 gene deletions," BMC Bioinformatics 1(1):1-10 (2000). | <input type="checkbox"/> |
| /KRS/ | 24 | Ellis et al., "The University of Minnesota Biocatalysis/Biodegradation Database: post-genomic data mining," Nucl. Acids. Res. 31(1):262-265 (2003).        | <input type="checkbox"/> |
| /KRS/ | 25 | Eppstein, "Finding the k Shortest Paths" in 35th IEEE Symp Foundations of Comp Sci, Santa Fe, pp. 154-165 (1994).  | <input type="checkbox"/> |
| /KRS/ | 26 | Fisher "The langragean relaxation method for solving integer programming," Manage. Sci. 27:1 (1981).   | <input type="checkbox"/> |
| /KRS/ | 27 | Geoffrion "Lagrangean relaxation and its uses in integer programming," Mat. Program. Stud. 2:82 (1974).  | <input type="checkbox"/> |

|   |                        |                         |
|---|------------------------|-------------------------|
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br>( Not for submission under 37 CFR 1.99) | Application Number     | 10616659                |
|   | Filing Date            | 2003-07-09              |
|   | First Named Inventor   | MARANAS, COSTAS D.      |
|   | Art Unit               | 1631                    |
|   | Examiner Name          | SKOWRONEK, KARLHEINZ R. |
|   | Attorney Docket Number | P06367US03 (1 OF 2)     |

|       |    |   |                          |
|-------|----|---|--------------------------|
| /KRS/ | 28 | Henriksen et al., "Growth energetics and metabolic fluxes in continuous cultures of <i>Penicillium chrysogenum</i> ," J. Biotechnol. 45:149-164 (1996).   | <input type="checkbox"/> |
| /KRS/ | 29 | Hugler et al., "Malonyl-coenzyme A reductase from <i>Chloroflexus aurantiacus</i> , a key enzyme of the 3-hydroxypropionate cycle for autotrophic CO(2) fixation," J. Bacteriol. 184(9):2404-2410 (2002). | <input type="checkbox"/> |
| /KRS/ | 30 | Hutchinson et al., "Global transposon mutagenesis and a minimal <i>Mycoplasma</i> genome," Science 286 (5447):2165-2169 (1999).   | <input type="checkbox"/> |
| /KRS/ | 31 | Itaya, "An estimation of minimal genome size required for life," FEBS Lett. 362(3):257-260 (1995).  | <input type="checkbox"/> |
| /KRS/ | 32 | Jorgensen, et al., "Metabolic flux distributions in <i>Penicillium chrysogenum</i> during fed-batch cultivations," Biotechnol. Bioeng. 46(2):117-131 (1995).  | <input type="checkbox"/> |
| /KRS/ | 33 | Kanehisa and Goto, "KEGG: kyoto encyclopedia of genes and genomes," Nucl. Acids Res. 28(1):27-30 (2000).  | <input type="checkbox"/> |
| /KRS/ | 34 | Kanehisa et al., "The KEGG resource for deciphering the genome," Nucl. Acids Res. 32(Database issue):D277-80 (2004).  | <input type="checkbox"/> |
| /KRS/ | 35 | KARP et al., "Eco Cyc: Encyclopedia of <i>Escherichia coli</i> genes and metabolism," Nuc. Acids Res. 27(1):55-58 (1999).   | <input type="checkbox"/> |
| /KRS/ | 36 | Karp et al., "The EcoCyc and MetaCyc databases," Nucl. Acids Res. 28(1):56-59 (2000).   | <input type="checkbox"/> |
| /KRS/ | 37 | Karp et al., "The EcoCyc Database," Nucl. Acids Res. 30(1):56-58 (2002).  | <input type="checkbox"/> |
| /KRS/ | 38 | Kataoka et al., "Studies of hydrogen production by continuous culture system of hydrogen-producing anaerobic bacteria," Wat. Sci. Tech. 36:41-47 (1997).  | <input type="checkbox"/> |

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**  
( Not for submission under 37 CFR 1.99)

|                        |                         |
|------------------------|-------------------------|
| Application Number     | 10616659                |
| Filing Date            | 2003-07-09              |
| First Named Inventor   | MARANAS, COSTAS D.      |
| Art Unit               | 1631                    |
| Examiner Name          | SKOWRONEK, KARLHEINZ R. |
| Attorney Docket Number | P06367US03 (1 OF 2)     |

|       |    |  |                          |
|-------|----|--|--------------------------|
| /KRS/ | 39 | Kauffman et al., "Advances in flux balance analysis," Curr. Opin. Biology. London, GB, 14(5):491-496 (2003).   | <input type="checkbox"/> |
| /KRS/ | 40 | KEASLING et al., "Engineering Polyphosphate Metabolism in Escherichia coli: Implications for Bioremediation of Inorganic Contaminants," Biotechnol. Bioeng. 58(2-3):321-239 (1998).  | <input type="checkbox"/> |
| /KRS/ | 41 | Korotkova et al., "Poly-beta-hydroxybutyrate biosynthesis in the facultative methylotroph methylobacterium extorquens AM1: identification and mutation of gap11, gap20, and phaR," J. Bacteriol. 184(22):6174-6181 (2002).   | <input type="checkbox"/> |
| /KRS/ | 42 | Krieger et al., "MetaCyc: a multiorganism database of metabolic pathways and enzymes," Nucl. Acids Res. 32 (Database issue), D438-D4342 (2004).  | <input type="checkbox"/> |
| /KRS/ | 43 | Lovley, "Cleaning up with genomics: applying molecular biology to bioremediation", Nat. Rev. Microbiol. 1(1):35-44 (2003).   | <input type="checkbox"/> |
| /KRS/ | 44 | Lutz et al., "Creating multiple-crossover DNA libraries independent of sequence identity," Proc. Natl. Acad. Sci. USA 98 (20):11248-11253 (2001).  | <input type="checkbox"/> |
|       | 45 | MARANAS, "Tightening Flux Balance Models Through Boolean Relations," American Institute of Chemical Engineers conference Proceedings, on <a href="http://www.aiche.org/conferences/techprogram/paperdetail.asp">http://www.aiche.org/conferences/techprogram/paperdetail.asp</a> , (retrieved 10-11-2002).<br>NOT AVAILABLE. | <input type="checkbox"/> |
| /KRS/ | 46 | Mavrovouniotis, et al., "Synthesis of Biochemical Production Routes," Comp. Chem. Engineer. 16:605-619 (1992).   | <input type="checkbox"/> |
| /KRS/ | 47 | MAVROVOUNIOTIS et al., "Computer-aided synthesis of biochemical pathways," Biotechnol. Bioeng. 36 (11):1119-1132 (1990).   | <input type="checkbox"/> |
| /KRS/ | 48 | MCSHAN et al., "PathMiner: predicting metabolic pathways by heuristic search," Bioinformatics. 19(13):1692-1698 (2003).  | <input type="checkbox"/> |
| /KRS/ | 49 | Methe et al., "Genome of Geobacter sulfurreducens: metal reduction in subsurface environments," Science 302 (5652):1967-9 (2003).  | <input type="checkbox"/> |

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**  
( Not for submission under 37 CFR 1.99)

|                        |                         |
|------------------------|-------------------------|
| Application Number     | 10616659                |
| Filing Date            | 2003-07-09              |
| First Named Inventor   | MARANAS, COSTAS D.      |
| Art Unit               | 1631                    |
| Examiner Name          | SKOWRONEK, KARLHEINZ R. |
| Attorney Docket Number | P06367US03 (1 OF 2)     |

|       |    |   |                          |
|-------|----|---|--------------------------|
| /KRS/ | 50 | Misawa et al., "Production of beta-carotene in Zymomonas mobilis and Agrobacterium tumefaciens by introduction of the biosynthesis genes from Erwinia uredovora," Appl. Environ. Microbiol. 57(6):1847-1849 (1991). | <input type="checkbox"/> |
|-------|----|---|--------------------------|

If you wish to add additional non-patent literature document citation information please click the Add button

**EXAMINER SIGNATURE**

|                    |                                    |                 |            |
|--------------------|------------------------------------|-----------------|------------|
| Examiner Signature | /Karlheinz Skowronek/ (06/22/2010) | Date Considered | 06/22/2010 |
|--------------------|------------------------------------|-----------------|------------|

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> See Kind Codes of USPTO Patent Documents at [www.USPTO.GOV](http://www.USPTO.GOV) or MPEP 901.04. <sup>2</sup> Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>3</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>4</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. <sup>5</sup> Applicant is to place a check mark here if English language translation is attached.

The line through references have not been considered because:

- 1)they are duplicates and of record (marked with \*) or
- 2)they were not supplied.